UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MOLLY F. KULESZ-MARTIN

Appeal No. 2005-2043
Application No. 08/644,289

ON BRIEF

Before ADAMS, MILLS, and GRIMES Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to vectors that contain DNA encoding an alternatively spliced variant of the tumor suppressor p53. The examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 134. Because we conclude that the examiner has not made out a prima facie case of obviousness, we reverse.

Background

The specification discloses that a previously known, "wild type alternatively spliced p53 (p53as, for alternative splice) RNA exists in cultured cells and normal tissue at approximately 30% of the major p53 RNA form. . . . The predicted protein encoded by the p53as transcript differs from p53 protein in 17 C-terminal amino acids and is

truncated by 9 amino acids due to alternative splicing of intron 10 of the wild type p53 gene." Page 1.

"In general, it can be stated that p53as is functionally the same as p53 except that a p53as lacks the negative regulatory domain for p53 sequence specific DNA binding which is found within the last 50 amino acids at the p53 C terminus. The negative regulatory domain of p53 negates p53 sequence specific binding in certain cellular environments which in turn causes p53 to lose activity. p53as lacks the negative regulatory domain and thus remains active in similar cellular environments." Page 3.

Discussion

1. Claim construction

Claims 1, 3-6, 8-11, 17, and 18 are on appeal. Claims 12-16 and 19 are also pending: the examiner has withdrawn claims 12-14 from consideration and has indicated that claims 15, 16, and 19 are allowable.

Claims 1 and 5 are representative of the claims on appeal and read as follows:

1. A plasmid containing a cDNA sequence which encodes a protein designated p53as, said p53as being sequentially the same as wildtype p53 up to the final 50 carboxy terminal amino acids of p53, said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 sequence specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, which negative regulatory domain must be activated in p53 for p53 to have active DNA binding, said p53as and activated p53 binding to the same p53 DNA binding sequence AGGCATGCCT/AGGCATGCCT, SEQ. I.D. NO. 5, and said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is reactive with the p53as but not with p53.

5. A viral vector containing a cDNA sequence which encodes a protein designated p53as, said p53as being sequentially the same as wildtype p53 up to the final 50 carboxy terminal amino acids of p53, said p53as being different than p53 within

the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain of p53 for p53 sequence specific DNA binding found within the last 50 amino acids at the p53 carboxy terminus, which negative regulatory domain must be activated in p53 for p53 to have active DNA binding, said p53as and activated p53 binding to the same p53 DNA binding sequence AGGCATGCCT/AGGCATGCCT, SEQ. I.D. NO. 5, and said p53as being different than p53 within the final 50 carboxy terminal amino acids of p53 so as to provide an epitope within said p53as which gives rise to an antibody which is reactive with the p53as but not with p53.

Thus, claims 1 and 5 are directed to as plasmid vector and viral vector, respectively, containing DNA that encodes a p53as protein, where the p53as protein has the following properties:

- The p53as amino acid sequence is identical to that of wild-type p53 up to the C-terminal 50 amino acids;
- The p53as amino acid sequence differs from wild-type p53 in the 50 C-terminal amino acids in such a way that it lacks the negative regulatory domain of wild-type p53;
- The p53as binds to the same DNA sequence that is bound by p53; and
- The difference in amino acid sequence in the C-terminal 50 amino acids results in formation of an epitope in p53as that is bound by an antibody that does not bind p53.

2. Obviousness in view of Han, Sambrook, Hupp, and Funk

The examiner rejected claims 1, 3, 4, and 17 under 35 U.S.C. § 103 on the basis that the claimed plasmid would have been obvious in view of Han,[1] Sambrook,[2] Hupp,[3] and Funk.[4] The examiner characterized Han as teaching fragments of cDNAs from alternatively spliced p53, which are cloned into plasmids for sequencing. See the

[1] Han et al., "Alternatively spliced p53 RNA in transformed and normal cells of different tissue types," Nucleic Acids Research, Vol. 20, pp. 1979-1981 (1992).
[2] Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Lab. Press (1989).
[3] Hupp et al., "Regulation of the specific DNA binding function of p53," Cell, Vol. 71, pp. 875-886 (1992).
[4] Funk et al., "A transcriptionally active DNA-binding site for human p53 protein complexes," Molecular and Cellular Biology, Vol. 12, pp. 2866-2871 (1992).

Examiner's Answer, page 5. The examiner acknowledged that Han "do[es] not teach a plasmid containing full length p53as cDNA," or "that p53as is different from p53 within the final 50 carboxy terminal amino acids of p53 so as to lack a negative regulatory domain," or "that said p53as . . . provide[s] an epitope within said p53as which gives rise to an antibody which is specific for p53as but not with p53." Id., page 6.

The examiner relied on Sambrook for "teach[ing] that expressing large amounts of proteins from cloned genes in plasmids is an art standard technique;" on Hupp for "teach[ing] that it is the C-terminus that inhibits DNA binding of wild type p53, and that removal of the 31 C-terminal amino acids constitutively activates p53;" and on Funk for teaching a DNA sequence bound by human p53. Id., pages 7-8.

The examiner concluded that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to clone a full length p53as cDNA into [a] plasmid" in order to "obtain a full length or intact native protein." Id., page 8. The examiner explained the motivation to do so as follows:

> To obtain full length, i.e. intact, native protein, such as full length p53as, expressed by plasmid containing full length cDNA for studying function of the protein, as suggested by Sambrook et al[.], or for studying biological characterization of the protein, as suggested by Han et al. Further, since the differences in the carboxy terminus between AS-p53 and R-53 [i.e., normally spliced p53] protein could lead to significant biochemical and biological changes, it is critical to include p53as in the study of the function of p53, as suggested by Han et al.

Appellants argue, in a nutshell, that "[t]his rejection is based upon an improper combination of references and even if the combination were proper, it would not disclose or suggest any embodiment of the presently claimed invention." Appeal Brief, page 8.

We will reverse the rejection. "In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). "[A] proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device . . . ; and (2) whether the prior art would also have revealed that in so making . . . , those of ordinary skill would have had a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991) (citation omitted).

In this case, we conclude that the examiner has not adequately shown that those skilled in the art would have been motivated to combine the cited references or that such a person would have reasonably expected to produce the claimed vectors if the references were combined. A suggestion to combine prior art teachings need not be express: possible sources include "the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1458 (Fed. Cir. 1998). "The question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination." Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984).

However, "[a]n element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. That motivation is not abstract, but practical and is always related to the properties or uses one skilled in the art would expect the compound to have, if made." In re Gyurik, 596 F.2d 1012, 1018, 201 USPQ 552, 557 (CCPA 1979).

Here, the examiner has not pointed to any properties that would have been expected for the p53as protein encoded by the claimed plasmid that would have led a person of ordinary skill in the art to expect that the protein would have a practical use. That is, the examiner's reasoning – that those skilled in the art would have been motivated to make large amounts of p53as in order to study the protein – does not state a reason sufficient to support a prima facie case under 35 U.S.C. § 103.

In addition, the examiner has not provided sufficient evidence that full-length p53as, even if cloned into a plasmid and expressed, would have all of the properties recited in claim 1. We note, in particular, the declaration filed under 37 CFR § 1.132 by Molly F. Kulesz-Martin (received January 2, 2003). In her declaration, Dr. Kulesz-Martin states that a form of p53 called p53-M8 has an amino acid sequence that differs at position 132 from that of the p53as exemplified in the instant specification. See page 3. Amino acid position 132 is not one of the C-terminal 50 amino acids. p53-M8 appears to be full-length alternatively spliced p53. See Figure 4 of Arai.[5] p53-M8 was isolated as a cDNA clone from transformed fibroblasts. See Arai, page 3233, right-hand column.

[5] Arai et al., "Immunologically distinct p53 molecules generated by alternative splicing," Molecular and Cellular Biology, Vol. 6, pp. 3232-3239 (1986). Arai was cited in the Information Disclosure Statement received August 26, 1996.

The p53as exemplified in the instant specification, by contrast, was created by combining part of normally spliced p53 and part of alternatively spliced p53. See pages 6-7:

> pBSp53as was constructed from p53 cDNA beginning at nt -111 . . . (where 1 is the first ATG encoding methionine) and ending at nt 1539, cloned into the EcoRI and BamHI sites of pBluescript SK. . . . The N-terminal fragment of wt p53 was amplified by reverse transcriptase/polymerase chain reaction (RT-PCR) . . . and the C-terminal fragment of p53as was amplified by PCR from plasmid p6.4 (which contains an alternatively spliced p53 cDNA; [citing Han]). . . . The C-terminal p53 cDNA (nt1028 to 1539) was amplified by PCR from plasmid p6.4. . . . The StuI to BamHI segment of this PCR reaction product was then ligated to the StuI and BamHI sites of plasmid pBSRS13 to create plasmid pBSp53as, containing a full length alternatively spliced p53 cDNA.

Thus, even if the examiner were correct that a person of ordinary skill in the art would have been motivated to clone the full-length, naturally occurring form of alternatively spliced p53, it appears from the evidence of record that that the naturally occurring form would not "be[ ] sequentially the same as wildtype p53 up to the final 50 carboxy terminal amino acids," as required by claim 1.

3. Obviousness in view of Han and Lee

The examiner rejected claims 5, 6, 8-11, and 18 under 35 U.S.C. § 103 on the basis that the claimed viral vector would have been obvious in view of Han and Lee.[6] The examiner again relies on Han for its teaching of cDNAs encoding part of alternatively spliced p53, and cites Lee for its teaching of baculovirus vectors. See the Examiner's Answer, pages 11-12. The examiner concluded that the references would have made it obvious to "use the baculovirus vector system of Lee et al[.] . . . as a vector for expressing . . . full length alternatively spliced p53 cDNA." Page 12. "The

motivation is to obtain full length, i.e. intact, biochemically active protein sequence, such as full length p53as, to study the properties of the protein, as suggested by Lee et al[.], or for studying biological characterization of the protein, as suggested by Han et al." Page 14.

For the same reasons discussed above, we conclude that the examiner has not adequately shown that those skilled in the art would have been led to combine Han and Lee or that the prior art would have provided a reasonable expectation of obtaining the product of claim 5. The rejection based on Han and Lee is reversed.

[6] Lee et al., EP 529160 A1, published March 3, 1993.

Summary

The examiner has not adequately shown that a person of ordinary skill in the art would have been motivated to combine the cited references or would have reasonably expected the combination, if made, to produce the claimed vectors. Since the examiner has not made out a prima facie case of obviousness, we reverse the rejections on appeal.

REVERSED

Donald E. Adams)
Administrative Patent Judge)
)
)
Demetra J. Mills) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
Eric Grimes) INTERFERENCES
Administrative Patent Judge)

EG/jlb

Michael L. Dunn
Simpson & Simpson, PC
5555 Main Street
Williamsville, NY 14221-5406